REMARKS

Formalities

Claims 1-29 have been canceled. Claims 30-35 have been added. The newly added claims do not add or constitute new matter. Support for the newly added claims may be found throughout the specification and originally filed claims. More particularly, support for the transgenic mouse, method of producing the mouse, cell obtained from the mouse, and methods of using the transgenic mouse as recited in the newly added claims may be found, for example, at page 3, line 23 through page 4, line 13, at page 7, lines 1-12, at page 10, line 10 through page 13, line 4, at page 13, line 12 through page 14, line 18, at page 15, lines 7-26 and at page 52, line 18 through page 54, line 13, of the specification. As such, no new matter has been added.

Amendments have been made to the specification to correct and/or update the Brief Description of the Drawings, and have merely deleted reference to portions of the Figures not actually present, which references were inadvertently included in the descriptions.

The amendment to the Figures, particularly Figure 1 and Figures 2A-2B, is made to incorporate the correct sequences, and is supported by the originally filed application. When originally filed, the sequence intended to be disclosed in these figures was mistakenly replaced with an incorrect sequence. However, the correct sequence is referred to in the specification (see page 2, lines 22-24 and page 7, lines 1-12), and the specification makes clear that this sequence was targeted for disruption by the invention disclosed therein. Therefore, no new matter was added by the amendment to the drawings.

The foregoing amendments are made solely to expedite prosecution of the instant application, and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Upon entry of the amendment, claims 30-35 are pending in the instant application.

Applicant respectfully requests reconsideration of the application in view of the amendments and remarks made herein.

Specification – Incorporation by Reference

The Examiner objected to the attempt to incorporate subject matter by reference to U.S. Non-provisional and Provisional applications (See page 10 and 11 of the specification). Applicant contends that the incorporation by reference to these applications is proper.

According to the MPEP, which describes guidelines for proper incorporation by reference, an application for patent may incorporate "essential material" by reference to "(1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application," subject to certain conditions. The "'essential material' may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application." See MPEP § 608.01(p).

Applicant submits that the attempts to incorporate material by reference satisfy these conditions. More particularly, Applicant attempted to incorporate by reference material from pending U.S. patent applications. In such cases, the MPEP states that, prior to allowance, if the referenced application has not been published or issued as a patent, Applicant will be required to amend the disclosure of the referencing application to include the material incorporated by reference, accompanied by an affidavit or declaration executed by the Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application.

However, Applicant submits that the material incorporated by reference in the instant application is not essential material, *i.e.* is not required in order to make the specification enabling. More particularly, the descriptions of the subject matter of the applications, which follow each attempt to incorporate the applications by reference (see page 10-11), are sufficient to enable the skilled artisan to practice the invention as claimed. As such, the Examiner's objection is improper, and Applicant requests that it be withdrawn.

Specification – Figures and Description of Figures

The Examiner has objected to the specification because the description of figures, the figures, and sequence listings do not match. Specifically, the description of figures refers to an amino acid sequence, which is not disclosed in Figure 1 or the sequence listing. Further, the sequence disclosed in SEQ ID NO:1 and in Figure 1 are not the same.

Applicant has deleted reference to an amino acid sequence in the description of Figure 1, which reference was mistakenly included in the description when filed. No amino acid sequence is disclosed in Figure 1, in the sequence listing, or in the specification. Further, the description of Figure 2B has been updated in order to recite the correct sequence identifiers (SEQ ID NO:2 and SEQ ID NO:3). In addition, Applicant has amended Figures 1 and 2A, both of which disclose and describe the sequence identified as SEQ ID NO:1. Applicant has filed a substitute sequence listing, which includes the 3 nucleic acid sequences disclosed in Figures 1-2(A and B).

Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures

The Examiner has stated that the instant application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. More particularly, the Examiner alleged that all of the sequences disclosed in the application are not identified by sequence identifiers in the Brief Description of the Drawings and are not included in the sequence listing.

Applicant has amended the drawings and the Brief Description of the Drawings in order to match sequences and sequence identifiers. Furthermore, Applicant submits concurrently herewith a substitute sequence listing, in paper and computer readable form, pursuant to 37 C.F.R. §1.821(c) and (e). The sequence listing includes all sequences disclosed in the instant application. Applicant submits that the content of the paper and computer readable copies of the sequence listing submitted herewith are the same. Moreover, as the sequence listing merely presents nucleotide sequences that appeared in or are supported by the application as originally filed in accordance with 37 C.F.R. §1.821-1.825, no new matter has been introduced into the application.

Applicant submits that the instant application is now compliant with the requirements set forth in 37 C.F.R. §§ 1.821-1.825.

Rejection under 35 U.S.C. § 101

The Examiner has rejected claims 8-12, 15 and 17-24 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility. Applicant respectfully traverses the rejection. Claims 8-12, 15 and 17-24 have been canceled. Applicant believes the rejection does not apply to new claims 30-35 for the reasons set forth below.

Claims 30-35 are drawn to a transgenic mouse whose genome comprises a disruption in a limulus clotting factor protease-like gene comprising the sequence set forth in SEQ ID NO:1,

which disruption results in a specific phenotype including increased sensitivity to pain and/or increased susceptibility to seizure, to a method of making the mouse, a cell isolated from the mouse, and to a method of using the mouse to identify agents capable of modulating the phenotypes.

The Examiner indicated that the utility rejection was based on a lack of disclosure by Applicant regarding the function of the sequence disclosed in SEQ ID NO:1 as a limulus clotting factor protease. The Examiner stated that Applicant did not provide any evidence or examples that the sequence encodes a protease, by sequence homology, functional assay, or other comparisons. The specification allegedly also fails to provide a correlation between the phenotypes exhibited by the claimed mice and the limulus clotting factor protease gene.

Applicant submits that the transgenic mouse and related methods and compositions as claimed are supported by a specific and substantial utility or well-established utility. More particularly, the specification demonstrates disruption of a gene comprising the sequence set forth in SEQ ID NO:1 in a mouse, which results in a specific phenotype of increased pain sensitivity and/or increased susceptibility to seizure. The transgenic mouse would clearly be useful for identifying agents capable of modulating the claimed phenotypes. The desire in the art for discovering treatments and methods of modulating pain and/or seizure establishes the claimed transgenic mice as having a well-established utility. The skilled artisan would recognize the utility and value of such an *in vivo* model for these conditions or disorders.

The Examiner's rejection of claims 8-12, 15 and 17-24 is no longer relevant as a result of the cancellation of these claims. Applicant submits that the rejection does not apply to newly submitted claims 30-35 for the reasons set forth above. Therefore, withdrawal of the rejection under 35 U.S.C. § 101 is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph - Enablement

The Examiner has rejected claims 8-12, 15 and 17-26 under 35 U.S.C. § 112, first paragraph, because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of either a specific or substantial asserted utility or a well-established utility set forth in the above utility rejection. Applicant respectfully traverses the rejection. However, in light of the cancellation of claims, and for the reasons set forth above in response to the utility rejection, Applicant submits that the rejection under 35 U.S.C. § 112, first

paragraph, for lack of utility has been overcome. Applicant respectfully requests withdrawal of this rejection.

The Examiner has also rejected claims 8-12, 15 and 17-26 under 35 U.S.C. § 112, first paragraph, because the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant respectfully traverses the rejection. Claims 8-12, 15 and 17-24 have been canceled.

Specifically, the Examiner has asserted that the specification fails to describe how to make a non-human transgenic animal (of any species), in that it fails to describe the phenotype resulting from disruption in any species, and such a phenotype is considered unpredictable in the art. Further, the Examiner asserts that the specification does not describe how to make any transgenic non-human animal with the claimed disruption because it fails to describe methods of using ES cells of species other than mouse in such a method. The Examiner has asserted that such ES cell technology, relating to culturing and maintaining ES cells in culture, was limited to the mouse system at the time of filing of the instant application. These aspects of the rejection do not apply to claims 30-35. More particularly, claims 30-35 overcome these aspects of the rejection by reciting a transgenic mouse, rather than a transgenic non-human animal, by reciting a phenotype resulting from the disruption of the target gene, and by reciting the use of embryonic stem cells in the methods of producing the transgenic mouse.

The Examiner has also asserted that Applicant has not sufficiently demonstrated that the phenotype exhibited by the claimed mice is a result of the disruption of the target sequence, and not a result of genetic variation. The Examiner has based this conclusion on the Lariviere reference (2001, *JPET,* Vol 297, pages 467-473), which the Examiner asserts establishes that the claimed phenotype, particularly of increased pain sensitivity, may be due to genetic variation and not to the disruption. Applicant traverses this aspect of the rejection. Lariviere *et al.* describe concerns related to the methods of studying phenotypes, particularly phenotypes related to nociception, hypersensitivity and analgesia, in knockout mice. More particularly, Lariviere *et al.* compared the responses of inbred mice, particularly of the 129P3/J (formerly 129/J) and C57BL/6J strains, to other inbred strains of mice, in tests relating to pain sensitivity.

Lariviere *et al.* suggest that the choice of mouse strains, typically 129 derived for the ES cell line and C57BL/6 derived for the breeding strain, as well as breeding strategies, lead to

possible misinterpretation of phenotypes related to pain. They base these conclusions on the observation that these two commonly combined strains have sometimes markedly different phenotypes in pain related studies. More particularly, Lariviere *et al.* observed that, in assays of thermal nociception, such as the Hot Plate Test, C57BL/6 mice were consistently more sensitive, showing shorter latencies to make a withdrawal response, when compared with the 129-derived mice (see page 469, second column, first full paragraph). They suggest that knockout mice may take on phenotypes resulting from the 129 strain background. The authors imply that when looking for a phenotype in a knockout mouse with a 129 ES cell and C57BL/6 breeding background, this discrepancy in pain sensitivity may lead to a misinterpretation of a "129-like" phenotype, or decreased sensitivity phenotype, for a disruption related phenotype. However, this theory does not apply to the instantly claimed mice, in that the claimed mice exhibit a C57BL/6-like, or increased pain sensitivity, phenotype. According to the authors, this type of phenotype is less likely due to the 129 strain background, or a hitchhiking donor gene. Lariviere *et al.* fail to provide any evidence or examples suggesting that the increased pain sensitivity phenotype, as observed by Applicant in the claimed mice, is a result of anything other than disruption of the target gene.

Applicant submits that the rejection under 35 U.S.C. § 112, first paragraph, for enablement, has been overcome as a result of the cancellation of claims and the arguments set forth above. Applicant respectfully requests withdrawal of the rejection. Applicant submits that claims 30-35 are patentable and fully meet the enablement requirements of 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, first paragraph – Written Description

The Examiner has rejected claims 8-12, 15 and 17-24 under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicant respectfully traverses the rejection. Claims 8-12, 15 and 17-24 have been canceled, and the rejection is no longer relevant to these claims.

The Examiner's rejection relates to the unpredictability of a phenotype of a transgenic animal, and the alleged failure of the specification to describe phenotypic (or other) consequences resulting from disruption of the target gene in a representative number of species of the genus of

non-human animals. The Examiner states that the art teaches that the phenotype of a transgenic mouse or animal cannot be predicted, and that genetically altered mice often exhibit unexpected phenotypes. Therefore, in order to meet the written description requirement, a phenotype needs to be described.

Applicant disagrees with the Examiner's conclusions. The rejection has been overcome as a result of the cancellation of claims 8-12, 15 and 17-24. New claims 30-35 relate to a transgenic mouse whose genome comprises a disruption in the target gene comprising SEQ ID NO:1, wherein the transgenic mice exhibit a phenotype of increased sensitivity to pain and/or increased susceptibility to seizure as a result of the disruption. As noted above, in order to comply with the written description requirements, Applicant needs to describe the phenotype of a transgenic mouse with the claimed disruption. Applicant submits that the specification has demonstrated that the transgenic mouse does exhibit a phenotype of increased pain sensitivity as a result of the disruption (see the arguments set forth above in response to the enablement rejection), as well as increased susceptibility to seizure. Briefly, Applicant demonstrated that the evidence and arguments cited by the Examiner (see the Lariviere reference) fail to provide a reason to suspect that the increased pain sensitivity phenotype was a result of anything other than disruption of the target gene. In particular, if the Examiner's arguments applied to the claimed mice, these mice would exhibit decreased sensitivity to pain, but, in fact, they exhibit the opposite phenotype. Thus, the theories relied on by the Examiner do not apply to the transgenic mice as claimed.

Applicant has overcome the Examiner's written description rejection by the cancellation of claims, and respectfully requests its withdrawal. Applicant submits that new claims 30-35 are patentable and fully meet the written description requirements as set forth in 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 10 and 15 under 35 U.S.C. § 112, second paragraph, for being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claims 10 and 15 have been canceled, and the rejection is no longer relevant.

More particularly, the Examiner asserted that claims 10 and 15 were indefinite because they are dependent on withdrawn claims. Applicant has overcome the rejection by the

cancellation of these claims. Applicant submits that the pending claims do not have improper dependencies on cancelled or withdrawn claims. Therefore, the rejection is no longer relevant.

Applicant submits that new claims 30-35 clearly point out and distinctly claim that regarded as the invention as required by the second paragraph of 35 U.S.C. § 112.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-387.

Respectfully submitted,

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